Journal of Plastic, Reconstructive & Aesthetic Surgery (2014) 67, 591—599

JPRAS
An International Journal of Surgical Reconstruction
www.JPRASurg.com

REVIEW

Thermo-sensitive TRP channels in peripheral nerve injury: A review of their role in cold intolerance

S. Kambiz [a,b,*,c], L.S. Duraku [a,b,c], J.C. Holstege [b], S.E.R. Hovius [a], T.J.H. Ruigrok [b], E.T. Walbeehm [a]

[a] *Department of Plastic, Reconstructive and Hand Surgery, Erasmus Medical Center, Rotterdam, The Netherlands*
[b] *Department of Neuroscience, Erasmus Medical Center, Rotterdam, The Netherlands*

Received 26 March 2013; accepted 17 December 2013

KEYWORDS
Transient receptor potential channel;
Peripheral nerve injury;
Neuropathic pain;
Thermal intolerance;
Cold intolerance

Summary One of the sensory complications of traumatic peripheral nerve injury is thermal intolerance, which manifests in humans mainly as cold intolerance. It has a major effect on the quality of life, and adequate therapy is not yet available. In order to better understand the pathophysiological background of thermal intolerance, we focus first on the various transient receptor potential (TRP) channels that are involved in temperature sensation, including their presence in peripheral nerves and in keratinocytes. Second, the role of thermo-sensitive TRP channels in cold and heat intolerance is described showing three different mechanisms that contribute to thermal intolerance in the skin: (a) an increased expression of TRP channels on nerve fibres and on keratinocytes, (b) a lower activation threshold of TRP channels and (c) the sprouting of non-injured nerve fibres. Finally, the data that are available on the effects of TRP channel agonists and antagonists and their clinical use are discussed.

In conclusion, TRP channels play a major role in temperature sensation and in cold and heat intolerance. Unfortunately, the available pharmaceutical agents that successfully target TRP channels and counteract thermal intolerance are still very limited. Yet, our focus should remain on TRP channels since it is difficult to imagine a reliable treatment for thermal intolerance that will not involve TRP channels.

* Corresponding author. Department of Plastic, Reconstructive and Hand Surgery, Erasmus Medical Center, Room EE.15.91, PO Box 2040, 3000 CA Rotterdam, The Netherlands. Tel.: +31 107043292; fax: +31 107044685.
E-mail addresses: s.kambiz@ersamusmc.nl, shoista.kambiz@gmail.com (S. Kambiz).
[c] Both authors contributed equally to this work.

1748-6815/$ - see front matter
http://dx.doi.org/10.1016/j.bjps.2013.12.014

Traumatic peripheral nerve injury in humans leads to a variety of motor and sensory deficits, depending on the severity of the lesion. Initially, functional (motor) recovery is of primary concern to patients and physicians, while sensory recovery receives less attention. However, at a later stage, attention may shift to sensory complications, such as thermal intolerance, also known as cold intolerance, which are often highly disabling and difficult to treat.[1] To clinicians, cold intolerance is the most common manifestation of neuropathic pain. Cold intolerance has been defined as "an exaggerated or abnormal reaction to cold exposure of the injured part causing discomfort or the avoidance of cold".[2] The highest incidence of cold intolerance is found in patients after peripheral nerve injury in the upper extremities (91%).[3] Cold intolerance is a ubiquitous problem in moderate to cold climates but, despite its high prevalence, its pathophysiology is largely unknown. In order to have a better understanding of the mechanism underlying thermal intolerance, we review the present data about temperature signalling under normal and pathologic conditions, with a focus on the thermal transducers called transient receptor potential (TRP) channels.

Temperature sensation

The sensation of temperature is transmitted by Aδ and C fibres, which terminate as free nerve endings in the skin.[4,5] Aδ fibres are thinly myelinated, relatively fast-conducting fibres with an average conduction velocity of about 12 m s^{-1},[6] whereas C fibres are non-myelinated, slowly conducting fibres with a conduction velocity of <0.8 m s^{-1}.[7] Aδ and C fibres are commonly referred to as nociceptive fibres as they are involved in conveying nociceptive information leading to pain, although non-nociceptive temperatures are also sensed by some of these fibres. All Aδ and C fibres terminate on neurons in the dorsal horn of the spinal cord, and some of these neurons in turn project to various brainstem nuclei and the thalamus. Three cortical areas are important for temperature sensation: the insula and the cingulate cortex for emotional processing and the somatosensory cortex for assessing the intensity and localisation of the stimulus[8,9] (Figure 1).

Temperature transduction

The receptors in the free nerve endings of Aδ and C fibres that are involved in temperature signalling were only recently discovered. They are TRP channels, which were named on the basis of their diminishing transient response to continuous light in mutant fruit flies (*Drosophila*).[10] Several subfamilies, defined by specific domains of the receptor have been identified. The currently known subfamilies are TRPV (vanilloid), TRPM (melastin), TRPA (acyrin), TRPN (no mechanoreceptor potential C), TRPP (polycystic), TRPML (mucolipin) and TRPC (canonical).[11] Most TRP receptors are polymodal, that is, sensitive to more than one modality (temperature, chemical, mechanical stimuli, etc.).[12] In the present review, we only discuss the thermo-sensitive TRP channels, namely the TRPV, TRPM and TRPA members.

Each thermo-sensitive TRP channel has a specific range of sensitivity for temperature (e.g., TRPV3: $\geq$34—38 °C, TRPM8: 25—28 °C, etc.), and together they are able to

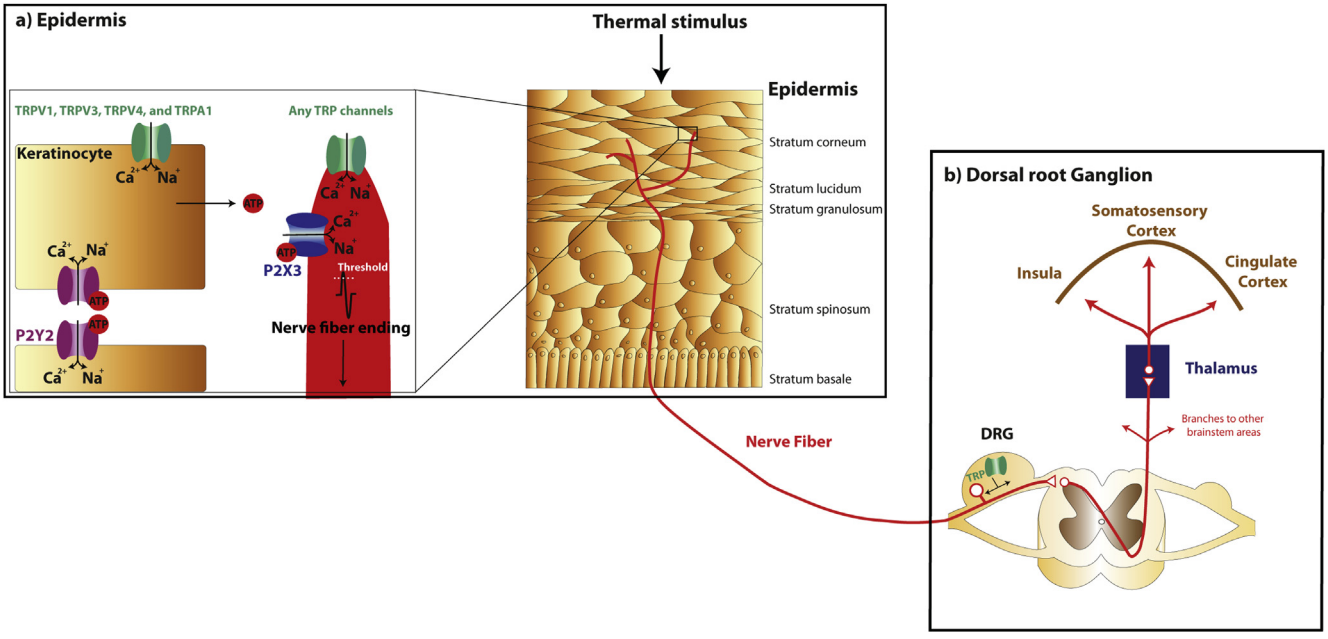

Figure 1 Thermal detection in the skin and transmission to the somatosensory cortex via the spinal cord. a) Epidermis: temperature is detected by the activation of TRP channels on keratinocytes and Aδ- and C-fibers in the skin. These channels allow an influx of sodium and calcium ions that initiates the generation of action potentials in the Aδ- and C-fibers. Keratinocytes communicate with adjacent nerve fibers by secreting ATP, which binds on P2X3 receptors. Expression of the P2X3 receptor on keratinocytes also enables an autocrine interaction between keratinocytes. b) The action potential from the Aδ- and C-fibers is transferred, via the dorsal root ganglion (DRG), where TRP channels are phosphorylated, to the cingulate cortex, the insula, and the somatosensory cortex with branches to other brainstem areas.